Efficient Syntheses of Oncinotine and Neooncinotine

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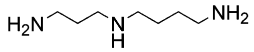
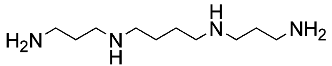
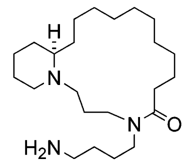
We have synthesized two natural alkaloids, oncinotine (**1**) and neooncinotine (**2**), by means of efficient ring-closing metathesis (RCM) reactions. The required dienes for RCM were assembled from three basic components: 2-allylpiperidine (**5**), 9-decenoic acid (**6**), and diamines **7**. We developed two different methods to achieve the linkage: the Michael addition of acrylamide and two amidations of succinic anhydride. The Grubbs catalyst was used to form the 17- and 18-membered lactams in 50% and 68% yields, respectively.

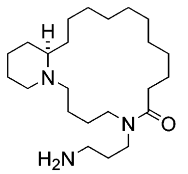
Introduction

Polyamines, such as spermidine and spermine, are present in a wide range of organisms from bacteria to plants and animals, and interest in these compounds is increasing because of their important role in cell growth.[1] Oncinotine (**1**) and neooncinotine (**2**), which can be isolated from the stem bark of Oncinotisnitida (Apocynaceae), belong to the spermidine group.[2,3] Both compounds are macrocyclic lactams fused with a piperidine unit and they differ only by the relative orientation of the spermidine moiety incorporated into the macrocyclic ring, i.e., oncinotine contains a 17-membered ring and a 4-aminobutyl side chain; on the other hand, neooncinotine has an 18-membered ring and a 3-aminopropyl side chain.


Spermidine


Spermine


(-)-Oncinotine


(-)-Neooncinotine

The Hesse and Schmid groups have both reported syntheses of these alkaloids, and Kibayashi's group has developed an enantioselective synthesis to (−)-oncinotine.[4,5] In these syntheses, the constructions of the macrocyclic rings were achieved through the formation of the amide bonds[4] or by reductive amination,[5] which meant that the preparation of lengthy carbon chains was inevitable and laborious. Multiple protections and deprotections were required, even though the final products contain only the functional groups associated with amines and lactams.

Recently, ring-closing metathesis (RCM) has evolved as a powerful tool for forming medium and large rings, which are rather difficult to prepare with more-conventional methods.[6] Applying RCM to the synthesis of the oncinotines provides a new route to the formation of the macrolactams in which the problems of the previous syntheses can be circumvented. Herein, we report our results regarding the use of ring-closing metathesis to prepare oncinotine and neooncinotine.

Scheme 1 displays our strategy toward these macrocyclic compounds. With the aim of using ring-closing

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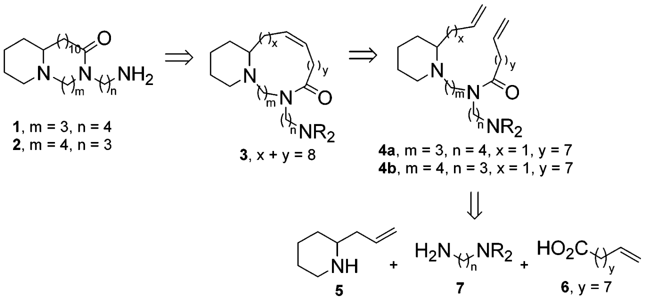
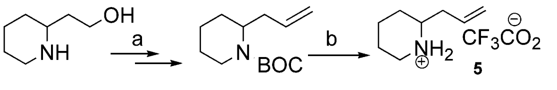
SCHEME 1. Retrosynthetic Analysis of 1 and 2



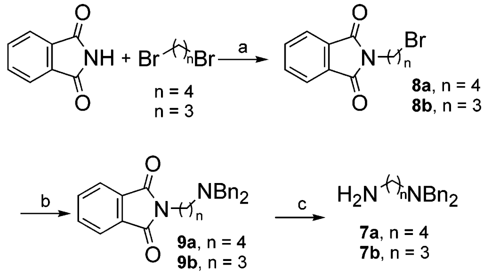
metathesis, the retrosyntheses of the oncinotines led to the alkenes **3** and their precursors, the dienes **4**. In fact, there are several possible combinations of dienes **4** that, in theory, can be used for RCM reactions, but we chose dienes **4a** and **4b** after taking the following points into consideration. It is known that the metathesis reaction is sensitive to the groups surrounding the olefins; for example, vicinal polar groups[7] and sterically hindered carbon atoms attached to the olefinic units usually retard metathesis reactions.[8] Therefore, a piperidine bearing a remote olefin side chain is preferred. Recent studies in ring-closing metathesis have shown that the Grubbs catalyst can tolerate homoallylic amines, such as those in **4a** and **4b**.[9] The accessibility of the substrates to form the dienes **4** is also an important factor. Since the length of the carbon chain in **3** is fixed (x + y = 8), the availability of both converging alkenes, the piperidine **5** and the alkenoic acid **6**, must be considered. After searching the literature, we found that methods for preparing 2-substituted alkenyl piperidines are rarer for molecules in which the terminal olefin is more distant from the piperidine unit.[10−13] In addition, commercial supplies of 8-nonenoic acid/alcohol and 7-octenoic acid/alcohol are very limited. In contrast, the key components of **4a** and **4b** are more easily obtained: the 2-allylpiperidine **5** has been reported by several groups,[11] and its counterpart alkene is derived from 9-decenoic acid (**6**).

SCHEME 2. Preparation of 5[a]



[a] Reagents and conditions: (a) ref 11a; (b) TFA, CH_2Cl_2, 99%.

SCHEME 3. Preparation of 7[a]



[a] Reagents and conditions: (a) K_2CO_3, $BnNEt_3Cl$, acetone, rt (**8a**: 75%; **8b**: 80%); (b) Bn_2NH, xylene, reflux, (**7a**: 75%; **7b**: 80%); (c) H_2NNH_2, EtOH, reflux (**7a**: 56%; **7b**: 54%).

Connecting diamines **7** and piperidine **5** with proper linkers leads to the spermidine moiety of these alkaloids, at which point the dienes **4a** and **4b** are ready for ring closure.

Results and Discussion

2-Allylpiperidine **5** was prepared from the commercially available 2-piperidineethanol by using a procedure based on that reported by Ikeda's group; the product was stored as its trifluoroacetate salt for further reactions (Scheme 2).[11a] The required decenoic acid **6** was prepared from the oxidation of 9-decenol.[14] We applied the Gabriel synthesis to form diamines **7**, as depicted in Scheme 3. After alkylating dibenzylamine with *N*-4-bromobutyl- and *N*-3-bromopropylphthalimides (**8a** and **8b**), we deprotected **9a**,**b** using hydrazine to give diamines **7a**,**b**.

With the three components in hand—the piperidine **5**, the diamines **7**, and the acid **6**—the next step was to connect these moieties with suitable methylene linkers to form dienes **4a**,**b**. Although synthetic methods to prepare linear polyamines such as spermidines have been developed,[15] we have found them difficult to apply when piperidine **5** and diamines **7** are present as subunits. We attempted several approaches, of which the following two routes proved to be effective (Schemes 4 and 5). The Michael addition of diamine **7a** to acrylamide **10** was the central step in the preparation of the precursor of oncinotine, diene **4a**. Thus, acrylamide **10**, prepared from piperidine **5** and acryloyl chloride, was heated under reflux with diamine **7a** to give the Michael adduct **11**. Amide **11** was then reduced with lithium aluminum hydride and coupled with acid **6** to give diene **4a**.

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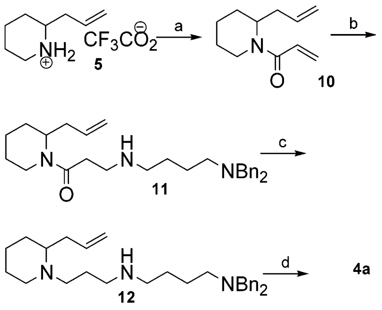
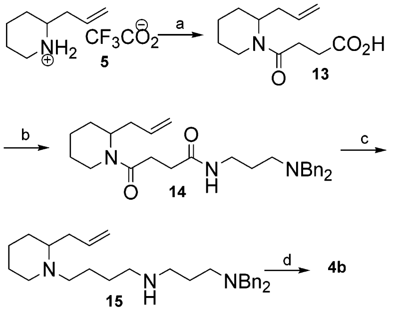
SCHEME 4. Synthesis of 4a[a]



[a] Reagents and conditions: (a) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 99%; (b) **7a**, toluene, reflux, 80%; (c) $LiAlH_4$, THF, reflux, 95%; (d) (i) **6**, $SOCl_2$, reflux; (ii) **12**, Et_3N, CH_2Cl_2, 0 °C, 86%.

SCHEME 5. Synthesis of 4b[a]



[a] Reagents and conditions: (a) succinic anhydride, K_2CO_3, DMF, rt, 91%; (b) **7b**, *N*,*N*'-diisopropylcarbodiimide, CH_2Cl_2, 82%; (c) $LiAlH_4$, THF, reflux, 96%; (d) (i) **6**, $SOCl_2$, reflux; (ii) **15**, Et_3N, CH_2Cl_2, 0 °C, 85%.

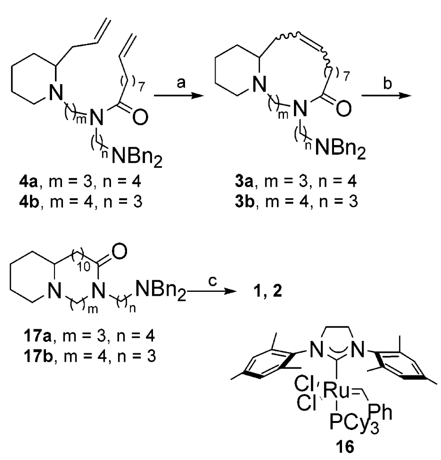
In contrast, we used succinic anhydride to provide the four bridging methylene units of **4b**, the precursor of neooncinotine. The acylation of piperidine **5** with succinic anhydride was achieved in high yield. The resulting carboxylic acid (**13**) was coupled with diamine **7b** by using *N*,*N*'-diisopropylcarbodiimide (DIC). The product diamide (**14**) was reduced to triamine **15**, which was coupled with **6** to form diene **4b**. Each of these transformations was accomplished in good yield.

In preparing the two precursors **4a**,**b**, we observed also the rotational isomers of amides **10**, **11**, **13**, **14**, **4a**, and **4b** in their NMR spectra.

The Grubbs' second-generation catalyst was used to achieve the ring closures.[16] Brown's group recently reported that ring-closing metatheses of amines can be performed under neutral or basic conditions,[9a] but we obtained the cyclized products **3a** and **3b** only under acidic conditions and heating under reflux in dichloromethane. These results are similar to those reported by the Grubbs and Wright groups.[9c,17] Both dienes **4a** and **4b** gave similar yields in their cyclizations, so it appears that the size of the ring, 17- or 18-membered, is not a critical issue here.

Hydrogenation of the lactams **3a** and **3b** at room temperature provided compounds **17a** and **17b**. As reported by Hesse and co-workers, the debenzylation of **17b** with H_2/Pd/C occurred only at elevated temperatures.[4b] ^1H NMR spectroscopy indicated that deprotection of **17a**,**b** over Pd/C did not reach completion, even after 4 h at 60 °C, and the concentrations of the impurities grew gradually as the reaction continued. Fortunately, debenzylation with Pearlman's catalyst, $Pd(OH)_2/C$, and ammonium formate gave cleaner products (**1** and **2**).[18] We also found that direct hydrogenations of alkenes **3a**,**b** using Pearlman's catalyst were not as clean as the products from the stepwise reactions.

SCHEME 6. Ring-Closing Metatheses To Form 1 and 2[a]



[a] Reagents and conditions: (a) Grubbs catalyst **16**, $HCl_{(aq)}$, CH_2Cl_2, reflux (**3a**: 50%; **3b**: 68%); (b) H_2, Pd/C (**17a**: 87%; **17b**: 99%); (c) NH_4CO_2H, $Pd(OH)_2/C$, ethanol, reflux (**1**: 74%; **2**: 70%).

In summary, we have developed efficient methods for the syntheses of oncinotine and neooncinotine. Only the preparations of diamines **7** and piperidine **5** involve protection/deprotection steps, and just six further steps were required to form these macrocyclic alkaloids once the three components **5**, **6**, and **7** were obtained. The total yields of oncinotine and neooncinotine from 2-piperidineethanol were 10% and 14%, respectively. These concise syntheses clearly show the merits of ring-closing metathesis for preparing macrocyclic compounds. Asymmetric versions of these syntheses should be feasible by incorporating the known chiral 2-(2-hydroxyethyl)piperidine as a starting material.[19]

Experimental Section

2-Allylpiperidine (5). Trifluoroacetic acid (3 mL) was added to a solution of *tert*-butyl 2-allylpiperidine-1-carboxylate (2.0 g, 8.87 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The excess trifluoroacetic acid and solvent were removed under vacuum to give the trifluoroacetate salt of **5** (2.13 g, 8.87 mmol, 99%). ^1H NMR ($CDCl_3$, 200 MHz) δ 1.45−1.57 (m, 2H), 1.71−1.92 (m, 4H), 2.26−2.48 (m, 2H), 2.60−3.05 (m, 2H), 3.29−3.36 (d, $J = 13.3$ Hz, 1H), 5.07−5.16 (m, 2H), 5.62−5.76 (m, 1H), 8.89 (br, 1H), 9.34 (br, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 130.3, 121.1, 57.3, 45.6, 37.8, 28.4, 22.2, 21.0. MS (CI) m/z 126 ($C_8H_{16}N$) $[M + H]^+$.

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***N*-(4-Bromobutyl)phthalimide (8a).** Phthalimide (5.88 g, 39.9 mmol), potassium carbonate (16.58 g, 120 mmol), and benzyltriethylammonium chloride (1.0 g, 4.4 mmol) were suspended in acetone (100 mL). 1,4-Dibromobutane (25.9 g, 14.5 mL, 120 mmol) was added to the suspension and then the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under vacuum and the residue was dissolved in water (70 mL) and CH_2Cl_2 (40 mL). The organic layer was separated and the aqueous solution was further extracted with CH_2Cl_2 (2 × 40 mL). The combined organic solution was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2; EtOAc/hexanes, 1:3; R_f 0.44) to provide **8a** (10.63 g, 37.6 mmol, 94%) as a colorless solid. Mp 72.5−74.0 °C. IR (neat) 2941, 1772, 1710, 1464, 1439, 718 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.77−1.99 (m, 4H), 3.36−3.42 (t, J = 6.3 Hz, 2H), 3.64−3.70 (t, J = 6.6 Hz, 2H), 7.64−7.71 (m, 2H), 7.75−7.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.1, 29.7, 32.7, 36.8, 123.1, 131.9, 133.8, 168.2. HRMS (FAB) calcd for $[M + H]^+$ ($C_{12}H_{13}BrNO_2$) 282.0130, found 282.0125. The spectroscopic data are consistent with those reported previously.[20]

***N*,*N*-Dibenzylbutane-1,4-diamine (7a).** A solution of phthalimide **8a** (3.0 g, 10.6 mmol) in xylene (30 mL) was added dropwise to a solution of dibenzylamine (4.6 g, 23.4 mmol) in xylene (30 mL) at 70 °C. After the addition was complete, the reaction mixture was heated under reflux for 20 h. The precipitated salt was filtered and the filtrate was concentrated. The crude oily product was purified by column chromatography (SiO_2: EtOAc/hexanes, 1:3; R_f 0.61) to provide *N*-(4-dibenzylaminobutyl)phthalimide (**9a**, 3.17 g, 7.9 mmol, 75%) as a light-yellow oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.37−1.75 (m, 4H), 2.44 (t, J = 6.2 Hz, 2H), 3.52 (s, 4H), 3.59 (t, J = 7.0 Hz, 2H), 7.18−7.35 (m, 10H), 7.65−7.70 (m, 2H), 7.79−7.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.4, 26.3, 37.8, 52.8, 58.3 (CH_2 × 5), 123.1, 126.7, 128.1, 128.7, 132.1, 133.8, 139.7, 168.4. HRMS (FAB) calcd for $[M + H]^+$ ($C_{26}H_{27}N_2O_2$) 399.2073, found 399.2079. A mixture of hydrazine monohydrate (0.40 g, 8.0 mmol) and **9a** (3.17 g, 8.0 mmol) in ethanol (30 mL) was heated under reflux for 3.5 h. After the mixture was cooled to room temperature, concentrated HCl (0.8 mL) was added, and the solution was then heated under reflux for another 1 h. The solvent was evaporated under vacuum and then saturated aqueous K_2CO_3 (100 mL) and diethyl ether (120 mL) were added to the residue. The insoluble material was removed and the organic layer was separated. The aqueous solution was extracted with diethyl ether (2 × 60 mL) and the combined organic phases were washed with saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH, 9:1; R_f 0.17) to provide **7a** (1.21 g, 4.5 mmol, 56%) as a colorless oil.[21] ^1H NMR ($CDCl_3$, 200 MHz) δ 1.37−1.50 (m, 4H), 1.81 (br, 2H), 2.40 (t, J = 6.8 Hz, 2H), 2.57 (t, J = 6.7 Hz, 2H), 3.52 (s, 4H), 7.16−7.37 (m, 10H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.2, 30.9, 41.7, 52.9, 58.1, 126.6, 127.9, 128.6, 139.7. HRMS (FAB) calcd for $[M + H]^+$ ($C_{18}H_{25}N_2$) 269.2018, found 269.2016.

***N*,*N*-Dibenzylpropane-1,3-diamine (7b).** *N*-(3-Bromopropyl)phthalimide (2.84 g, 10.6 mmol) dissolved in xylene (30 mL) was added dropwise to a solution of dibenzylamine (4.6 g, 23.4 mmol) in xylene (30 mL) at 70 °C. After the addition was complete, the reaction mixture was heated under reflux for 20 h. The precipitated salt was filtered and the filtrate was concentrated. The crude product was purified by recrystallization from EtOAc/hexanes to provide *N*-(3-dibenzylaminopropyl)phthalimide (**9b**, 3.26 g, 8.4 mmol, 80%) as a colorless solid.[22] Mp 107.5−110.0 °C. IR (neat) 3374, 3293, 3072, 2941, 2790, 1491, 1455, 740, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.84−1.91 (m, 2H), 2.49 (t, J = 6.8 Hz, 2H), 3.56 (s, 4H), 3.67 (t, J = 7.5 Hz, 2H), 7.14−7.31 (m, 10H), 7.64−7.69 (m, 2H), 7.75−7.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.7, 36.1, 50.2, 58.0, 122.9, 126.7, 128.0, 128.7, 132.0, 133.6, 139.2, 168.2. HRMS (FAB) calcd for $[M + H]^+$ ($C_{25}H_{25}N_2O_2$) 385.1916, found 385.1913. A mixture of hydrazine monohydrate (0.76 g, 15.7 mmol) and **9b** (5.03 g, 13.1 mmol) in ethanol (30 mL) was heated under reflux for 3.5 h. After the reaction mixture was cooled to room temperature, concentrated HCl (1.4 mL) was added, and the solution was heated under reflux for another 1 h. The solvent was evaporated under vacuum and then saturated aqueous K_2CO_3 (200 mL) and diethyl ether (200 mL) were added to the mixture. The insoluble material was removed and the organic layer was separated. The aqueous solution was extracted with diethyl ether (2 × 60 mL) and the combined organic phases were washed with saturated aqueous NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH, 9:1; R_f 0.45) to provide **7b** (1.81 g, 7.1 mmol, 54%) as a colorless oil.[21] ^1H NMR ($CDCl_3$, 500 MHz) δ 1.65−1.70 (m, 2H), 1.97 (br, 2H), 2.49 (t, J = 6.7 Hz, 2H), 2.73 (t, J = 6.7 Hz, 2H), 3.7 (s, 4H), 7.25−7.29 (m, 2H), 7.30−7.39 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.4, 40.0, 50.7, 58.4, 126.9, 128.2, 128.9, 139.7. HRMS (FAB) calcd for $[M + H]^+$ ($C_{17}H_{23}N_2$) 255.1861, found 255.1858.

***N*-Acryloyl-2-allylpiperidine (10).** Triethylamine (260 μL, 1.84 mmol) and acryloyl chloride (35 μL, 0.44 mmol) were added sequentially to a solution of piperidine **5** (46 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred for another 30 min at 0 °C and then warmed to room temperature. The mixture was diluted with CH_2Cl_2 (20 mL), washed with 1 N HCl (2 × 10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: EtOAc; R_f 0.66) to provide **10** (65 mg, 0.37 mmol, 99%) as a light-yellow oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.32−1.34 (br, 1H), 1.54−1.62 (m, 5H), 2.08 (m, 1H), 2.21−2.26 (br, 1H), 2.61 and 3.03 (br, 1H), 3.70 and 4.47 (br, 1H), 4.02 and 4.82 (br, 1H), 4.96 (br, 2H), 5.54 (d, J = 10.8 Hz, 1H), 5.63 (br, 1H), 6.12 (d, J = 16.5 Hz, 1H), 6.45−6.47 (br, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamers) 18.8, 25.2, 26.1, 27.1, 28.7, 34.2, 34.8, 36.9, 41.4, 47.8, 53.0, 116.7, 117.9, 126.8 ($COCH{=}CH_2$), 128.6 ($COCH{=}CH_2$), 134.2, 135.2, 165.9. HRMS (FAB) calcd for $[M + H]^+$ ($C_{11}H_{18}NO$) 180.1388, found 180.1385.

1-{3-[4-(Dibenzylaminobutyl)amino]propionyl}-2-allylpiperidine (11). A mixture of diamine **7a** (265 mg, 0.98 mg) and piperidine **10** (117 mg, 0.98 mmol) in toluene (5 mL) was heated under reflux for 32 h. The solvent was evaporated under vacuum and the crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH, 9:1; R_f 0.23) to provide the title compound **11** (348 mg, 0.77 mmol, 79%) as a light-yellow oil. IR (neat) 2930, 2860, 2797, 1637, 1458, 915, 741, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.27 (br, 1H), 1.56−1.69 (m, 9H), 2.29−2.36 (m, 2H), 2.37−2.46 (m, 3H), 2.55−2.65 (m, 4H), 2.89 (br, 1H), 3.55 (s, 4H), 2.80 and 3.05 (br, 1H), 3.61 and 4.55 (br, 1H), 3.90 (br, 1H, NH), 5.00−5.12 (m, 2H), 5.71−5.74 (m, 1H), 7.21−7.24 (m, 2H), 7.30−7.33 (m, 4H), 7.36−7.37 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamers) 170.2, 170.3, 139.8, 135.2, 134.2, 128.8, 128.2, 126.8, 118.1, 116.8, 58.3, 52.9, 52.6, 49.4, 47.5, 45.4, 45.3, 41.0, 36.5, 34.6, 34.2, 32.5,32.3, 28.4, 27.2, 26.8, 26.0, 25.3, 24.7, 18.8. HRMS (FAB) calcd for $[M + H]^+$ ($C_{29}H_{42}N_3O$) 448.3328, found 448.3328.

1-{3-[4-(Dibenzylaminobutyl)amino]propyl}-2-allylpiperidine (12). $LiAlH_4$ (50 mg, 1.2 mmol) was added to a solution of compound **11** (54 mg, 0.12 mmol) in THF, which was then heated under reflux for 3 h. The reaction mixture

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was diluted with diethyl ether (30 mL) and quenched with water (0.5 mL) and saturted aqueous Na_2CO_3 (1 mL). The organic solution was decanted and concentrated to give the product **12** (47 mg, 0.11 mmol, 90%) as a colorless oil. IR (neat) 3026, 2927, 2854, 2792, 1454, 1025, 910, 740, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (m, 1H), 1.30−1.45 (m, 7H), 1.45−1.74 (m, 4H), 2.10−2.24 (m, 2H), 2.24−2.39 (m, 4H), 2.40 (m, 2H), 2.48 (m, 2H), 2.54 (m, 2H), 2.70 (m, 1H), 2.82 (m, 1H), 3.51 (s, 4H), 4.99−5.04 (m, 2H), 5.73−5.79 (m, 1H), 7.17−7.20 (m, 2H), 7.24−7.28 (m, 4H), 7.33−7.34 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.3, 24.9, 25.6, 25.7, 27.5, 30.4, 35.6, 49.0, 50.0, 51.5, 52.1, 53.2, 58.4, 59.8, 116.5, 126.8, 128.2, 128.8, 135.9, 140.0. HRMS (FAB) calcd for $[M + H]^+$ ($C_{29}H_{44}N_3$) 434.3535, found 434.3537.

4-Oxo-4-(2-allylpiperidino)butyric Acid (13). Anhydrous K_2CO_3 (380 mg, 2.76 mmol) was added to a solution of piperidine **5** (23 mg, 0.18 mmol) and succinic anhydride (55 mg, 0.55 mmol) in DMF (2 mL). After the mixture was stirred at room temperature for 24 h, diethyl ether (20 mL) and water (5 mL) were added to the suspension. The organic layer was separated and the aqueous solution was further extracted with diethyl ether (2 × 10 mL). The combined ether phases were washed with 1 N HCl (2 × 10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated to provide the acid **13** (37 mg, 0.17 mmol, 91%) as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (rotamer) 1.17 (br, 1H), 1.48−1.72 (m, 5H), 2.18−2.40 and 2.40−2.52 (m, 2H), 2.62 (m, 4H), 2.62 (m) and 3.07 (dt, $J = 13.5$, Hz, $J = 2.4$ Hz, 1H), 3.62 (d, $J = 13.2$ Hz) and 4.49 (d, $J = 13.4$ Hz, 1H), 3.97 (br) and 4.80 (dd, $J = 12.9$, Hz, $J = 6.9$ Hz,1H), 4.96−5.10 (m, 2H), 5.64−5.70 (m, 1H), 8.94 (br, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamer) 18.7, 18.8, 25.3, 25.9, 27.2, 28.3, 28.4, 28.5, 28.8, 30.0, 34.2, 34.6, 37.1, 41.1, 48.1, 52.9, 116.9, 118.3, 134.0, 135.0, 170.7, 170.8, 176.5, 176.6. HRMS (FAB) calcd for $[M + H]^+$ ($C_{12}H_{20}NO_3$) 226.1443, found 226.1461.

***N*-(3-Dibenzylaminopropyl)-4-oxo-4-(2-allylpiperidinyl)-butyramide (14).** 1,3-Diisopropylcarbodiimide (410 μL, 2.63 mmol) was added to a solution of acid **13** (456 mg, 2.02 mmol) and diamine **7b** (515 mg, 2.02 mmol) in CH_2Cl_2 (30 mL). After the solution was stirred at room temperature for 24 h, the solvent was evaporated and the crude product was purified by column chromatography (SiO_2: EtOAc; R_f 0.56) to provide the diamide **14** (76 mg, 0.16 mmol, 82%) as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (m, 1H), 1.63−1.70 (m, 8H), 2.22−2.42 (m, 3H), 2.42−2.52 (m, 3H), 2.55−2.64 (m, 2H), 2.48 (m) and 3.10 (t, $J = 13.4$ Hz, 1H), 3.68 (d, $J = 12.9$ Hz) and 4.52 (d, $J = 13.5$ Hz, 1H), 4.03 (m) and 4.85 (m, 1H), 5.00−5.14 (m, 2H), 5.72 (m, 1H), 6.0 (br, 1H), 7.28−7.38 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamer) 18.8, 25.4, 26.0, 26.2, 26.3, 27.2, 28.4, 28.9, 29.2, 31.6, 34.2, 34.6, 36.7, 37.5, 37.6, 40.9, 47.6, 50.3, 50.4, 52.4, 58.5, 116.7, 118.0, 127.1, 127.2, 128.3, 128.4, 129.0, 134.3, 135.3, 139.5, 170.4, 170.5, 171.9, 172.4. HRMS (FAB) calcd for $[M + H]^+$ ($C_{29}H_{40}N_3O_2$) 462.3121, found 462.3128.

1-{3-[4-(Dibenzylaminopropyl)amino]butyl}-2-allylpiperidine (15). $LiAlH_4$ (1.53 g, 38.2 mmol) was added to a solution of diamide **14** (1.76 g, 3.8 mmol) in THF (30 mL). After the solution was heated under reflux for 3 h, diethyl ether (50 mL) was added to the reaction mixture, which was quenched with water (5 mL) and saturated aqueous Na_2CO_3 (5 mL). The white precipitate was filtered and the filtrate was concentrated to give triamine **15** (1.42 g, 3.3 mmol, 87%) as a light-yellow oil. IR (neat) 3302, 3072, 3028, 2944, 2791, 1498, 1449, 1124, 991, 966, 911, 740, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (br, 1H), 1.38−1.55 (m, 7H), 1.55−1.62 (m, 2H), 1.62−1.72 (m, 2H), 2.11−2.25 (m, 2H), 2.25−2.40 (m, 4H), 2.43 (m, 2H), 2.49 (m, 2H), 2.52−2.69 (m, 3H), 2.78 (br, 1H), 3.51 (s, 4H), 5.00−5.03 (m, 2H), 5.73−5.80 (m, 1H), 7.18−7.21 (m, 2H), 7.24−7.38 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.3, 23.5, 25.7, 26.9, 28.2, 30.4, 35.7, 48.0, 50.0, 51.3, 51.8, 53.6, 58.4, 60.0, 116.4, 126.9, 128.1, 128.2, 128.4, 128.8, 136.0, 139.8. HRMS (FAB) calcd for $[M + H]^+$ ($C_{29}H_{44}N_3$) 434.3535, found 434.3546.

Diene 4a. A mixture of 9-decenoic acid (115 mg, 0.68 mmol) and thionyl chloride (0.5 mL, 6.85 mmol) was heated under reflux in a 25-mL flask at 60 °C for 30 min. The excess thionyl chloride was evaporated under vacuum and additional CH_2Cl_2 (2 mL) was added. The solution of 9-decenoyl chloride was added by syringe to a solution of **12** (250 mg, 0.56 mmol) and triethylamine (120 μL, 0.85 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred at 0 °C for another 1 h, the reaction mixture was warmed to room temperature, diluted with CH_2Cl_2 (20 mL), washed with water (2 × 10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH, 9:1; R_f 0.50) to provide **4a** (228 mg, 0.39 mmol, 70%) as a light-yellow oil. IR (neat) 3028, 2928, 2855, 1643, 1456, 994, 911,740, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.27−1.31 (m, 8H), 1.37−1.38 (m, 3H), 1.49−1.50 (m, 3H), 1.60−1.62 (m, 4H), 1.74 (br, 2H), 1.87 (br, 2H), 2.04 (m, 3H), 2.21−2.27 (m, 4H), 2.35−2.65 (m, 3H), 2.65−3.14 (br, 3H), 3.14−3.29 (m, 4H), 3.56 (s, 4H), 4.93−5.14 (m, 4H), 5.79−5.84 (m, 2H), 7.23−7.26 (m, 2H), 7.29−7.37 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamers) 178.4, 173.3, 172.8, 139.8, 139.6, 139.2, 139.1, 135.1, 133.8, 128.8, 128.7, 128.2, 128.1, 126.9, 126.8, 118.3, 117.2, 114.2, 114.1, 59.78, 59.5, 58.5, 58.3, 53.2, 53.0, 50.6, 50.2, 49.8, 49.4, 47.9, 45.8, 45.6, 43.5, 35.8, 34.3, 33.8, 33.6, 33.2, 33.1, 29.7, 29.5, 29.4, 29.3, 29.0, 28.9, 27.1, 26.6, 25.6, 25.5, 25.4, 24.9, 25.5, 24.4, 22.8, 22.7, 22.1, 21.2. HRMS (FAB) calcd for $[M + H]^+$ ($C_{39}H_{60}N_3O$) 586.4736, found 586.4734.

Diene 4b. A mixture of 9-decenoic acid (156 mg, 0.92 mmol) and thionyl chloride (0.15 mL, 2.06 mmol) was heated under reflux in a 25-mL flask at 60 °C for 30 min. The excess thionyl chloride was evaporated under vacuum and additional CH_2Cl_2 (2 mL) was added. The solution of 9-decenoyl chloride was added by syringe to a solution of **15** (266 mg, 0.61 mmol) and triethylamine (250 μL, 1.82 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred at 0 °C for another 1 h, the reaction mixture was warmed to room temperature, diluted with CH_2Cl_2 (20 mL), washed with water (2 × 10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH, 9:1; R_f 0.55) to provide **4b** (245 mg, 0.42 mmol, 85%) as a light-yellow oil. IR (neat) 3029, 2928, 2854, 1642, 1457, 994, 911,740, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28−1.36 (br, 11H), 1.46 (m, 3H), 1.50−1.82 (br, 8H), 2.03−2.04 (m, 2H), 2.21−2.40 (m, 4H), 2.40−2.61 (m, 4H), 2.61−3.02 (m, 3H), 3.02−3.20 (m, 2H), 3.20−3.32 (m, 2H), 3.57 (s, 4H), 4.93−5.09 (m, 4H), 5.78−5.82 (m, 2H), 7.22−7.36 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamers) 172.9, 172.7, 139.7, 139.3, 139.2, 139.1, 135.4, 134.6, 128.8, 128.7, 128.3, 128.2, 127.1, 126.8, 117.6, 117.0, 114.2, 114.1, 59.6, 59.5, 58.7, 58.4, 52.7, 52.2, 51.2, 51.0, 50.9, 48.3, 47.9, 46.1, 45.1, 44.3, 41.3, 36.8, 36.4, 35.0, 34.6, 33.8, 33.7, 33.2, 31.9, 29.5, 29.4, 29.3, 29.1, 28.9, 28.8, 27.2, 25.9, 25.7, 25.5, 25.4, 25.3, 22.7, 21.8. HRMS (FAB) calcd for $[M + H]^+$ ($C_{39}H_{60}N_3O$) 586.4736, found 586.4732.

Lactam 3a. Concentrated HCl (10 drops) was added to a solution of diene **4a** (177 mg, 0.30 mmol) and Grubbs catalyst **15** (25.6 mg, 0.03 mmol) in CH_2Cl_2 (70 mL). Nitrogen was bubbled through the solution for 10 min before the reaction mixture was heated under reflux for 24 h. The solution was poured into a separation funnel and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and saturated aqueous NaCl (10 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH, 9:1; R_f 0.48) to provide **3a** (84 mg, 0.15 mmol, 50%) as a brown oil. IR (neat) 3028, 2930, 2855, 1642, 1459, 970, 741, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15−1.35 (m, 11H), 1.35−1.50 (br, 3H), 1.50−1.70 (m, 8H), 1.78−2.05 (m, 4H), 2.05−2.51 (m, 7H), 2.51−2.98 (br, 2H), 3.11−3.20 (m, 4H), 3.52 (s, 4H), 5.41−5.43 (m, 2H), 7.18−7.86 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamer) 173.6, 173.0, 172.9, 139.6, 139.2, 129.1, 129.0, 128.8, 128.3, 128.2, 127.1, 127.0, 58.8, 58.5, 53.2, 53.1, 52.7, 51.9, 51.1, 51.0, 50.9, 48.4, 48.3, 46.2, 45.8, 44.2, 35.5, 35.1, 33.1, 32.8, 32.7, 31.8, 29.7, 28.8, 28.5, 28.1, 27.9, 27.6, 27.4, 27.3, 27.2, 27.0, 26.9, 26.2, 26.3, 26.1, 25.5, 25.4, 25.0, 22.5. HRMS (FAB) calcd for $[M + H]^+$ ($C_{37}H_{56}N_3O$) 558.4423, found 558.4426.

Lactam 3b. Concentrated HCl (10 drops) was added to a solution of diene **4b** (240 mg, 0.41 mmol) and Grubbs catalyst **16** (35 mg, 0.04 mmol) in CH_2Cl_2 (100 mL) and then N_2 gas was bubbled through the solution for 10 min. The reaction mixture was then heated under reflux for 24 h. The solution was poured into a separation funnel and washed with saturated aqueous $NaHCO_3$ (10 mL × 2) and saturated aqueous NaCl (10 mL). The organic layer was collected, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH, 9:1; R_f 0.55) to provide **3b** (156 mg, 0.3 mmol, 68%) as a brown oil. IR (neat) 3027, 2928, 2853, 1639, 1455, 969, 740, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15−1.35 (m, 11H), 1.35−1.50 (br, 3H), 1.50−1.70 (m, 8H), 1.78−2.05 (m, 4H), 2.05−2.51 (m, 7H), 2.51−2.98 (br, 2H), 3.11−3.20 (m, 4H), 3.52 (s, 4H), 5.41−5.43 (m, 2H), 7.18−7.86 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamer) 173.6, 173.0, 172.9, 139.6, 139.2, 129.1, 129.0, 128.8, 128.3, 128.2, 127.1, 127.0, 58.8, 58.5, 53.2, 53.1, 52.7, 51.9, 51.1, 51.0, 50.9, 48.4, 48.3, 46.2, 45.8, 44.2, 35.5, 35.1, 33.1, 32.8, 32.7, 31.8, 29.7, 28.8, 28.5, 28.1, 27.9, 27.6, 27.4, 27.3, 27.2, 27.0, 26.9, 26.2, 26.3, 26.1, 25.5, 25.4, 25.0, 22.5. HRMS (FAB) calcd for $[M + H]^+$ ($C_{37}H_{56}N_3O$) 558.4423, found 558.4426.

Lactam 17a. Concentrated HCl (1 drop) was added to a mixture of lactam **3a** (12.9 mg, 0.02 mmol) and Pd/C (5% w/w, 4 mg) in MeOH (1 mL). The flask was placed into an autoclave and the mixture was reacted under H_2 (20 atm) for 5 h. The Pd/C and methanol were removed by filtration and under vacuum, respectively. The residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated to give oily **17a** (11.2 mg, 0.02 mmol, 87%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23−1.46 (m, 20H), 1.23−1.95 (m, 10H), 2.15−2.34 (m, 4H), 2.42 (br, 3H), 2.50−2.69 (br, 1H), 2.80−2.95 (br, 1H), 2.95−3.38 (m, 4H), 3.53 (s, 4H), 7.14−7.33 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamer) 173.6, 173.0, 172.9, 139.8, 139.2, 129.1, 129.0, 128.8, 128.3, 128.2, 127.0, 126.8, 58.8, 58.5, 53.2, 53.1, 52.7, 51.9, 51.1, 51.0, 50.9, 48.4, 48.3, 46.2, 45.8, 44.2, 35.5, 35.1, 33.1, 32.8, 32.7, 31.8, 29.7, 28.8, 28.6, 28.1, 27.9, 27.6, 27.4, 27.3, 27.2, 27.0, 26.9, 26.6, 26.3, 26.1, 25.5, 25.4, 25.0, 25.5. HRMS (FAB) calcd for $[M + H]^+$ ($C_{37}H_{58}NO_3$) 560.4580, found 560.4578.

Lactam 17b. Concentrated HCl (1 drop) was added to a mixture of lactam **3b** (12.7 mg, 0.02 mmol) and Pd/C (5% w/w, 4 mg) in MeOH (1 mL). The flask was placed into an autoclave and then the mixture was reacted under H_2 (20 atm) for 5 h. The Pd/C and methanol were removed by filtration and under vacuum, respectively. The residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated to give oily **17b** (12.1 mg, 0.02 mmol, 99%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22−1.50 (m, 14H), 1.50−1.75 (m, 6H), 1.75−1.95 (m, 4H), 1.95−2.13 (br, 2H), 2.13−2.35 (m, 4H), 2.39 (m, 3H), 2.48−2.98 (br, 2H), 2.98−3.25 (br, 4H), 3.50 (s, 4H), 5.34−5.47 (m, 2H), 7.16−7.22 (m, 2H), 7.24−7.49 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (rotamer) 173.6, 172.9, 172.6, 139.8, 139.6, 128.6, 128.1, 128.0, 126.7, 126.6, 58.4, 58.2, 53.1, 52.9, 52.2, 51.9, 51.1, 50.2, 47.7, 47.2, 46.5, 46.1, 45.5, 45.3, 35.4, 34.9, 33.1, 32.8, 32.6, 31.3, 29.4, 28.7, 27.9, 27.8, 27.5, 27.4, 27.0, 26.9, 28.8, 26.7, 26.5, 26.2, 26.0, 25.4, 24.4, 23.4. HRMS (FAB) calcd for $[M + H]^+$ ($C_{37}H_{56}N_3O$) 558.4423, found 558.4436.

Oncinotine (1). A mixture of lactam **17a** (20.1 mg, 0.036 mmol), $Pd(OH)_2/C$ (20% w/w, 6 mg), and ammonium formate (22.6 mg, 0.36 mmol) in ethanol (3 mL) was heated under reflux for 18 h. The ethanol was evaporated under vacuum then CH_2Cl_2 (10 mL) was added to the residue. The palladium catalyst was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH/concentrated NH_4OH, 40:9:1; R_f 0.63) to provide **1** (10.0 mg, 0.026 mmol, 74%) as a light-yellow oil. IR (neat) 2929, 2855, 1642, 1461, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23−1.35 (m, 17H), 1.47−1.75 (m, 10H), 1.75−2.0 (br, 3H), 2.20−2.29 (m, 3H), 2.30−3.01 (m, 8H), 3.01−3.28 (m, 4H).[5a] HRMS (FAB) calcd for $[M + H]^+$ ($C_{23}H_{46}N_3O$) 380.3641, found 380.3653.

Neooncinotine (2). A mixture of lactam **17b** (14.8 mg, 0.026 mmol), $Pd(OH)_2/C$ (20% w/w, 5 mg), and ammonium formate (16.4 mg, 0.26 mmol) in ethanol (3 mL) was heated under reflux for 19 h. The ethanol was evaporated under vacuum and then CH_2Cl_2 (10 mL) was added to the residue. The palladium catalyst was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography (SiO_2: $CHCl_3$/MeOH/concentrated NH_4OH, 40:9:1; R_f 0.65) to provide **2** (7.0 mg, 0.018 mmol, 70%) as a light-yellow oil. IR (neat) 2928, 2855, 1641, 1461, 733 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (m, 6H), 1.29−1.45 (m, 10H), 1.45−1.78 (m, 10H), 1.81 (m, 1H), 1.85−2.02 (m, 1H), 2.02−2.50 (br, 5H), 2.50−3.00 (br, 6H), 3.01−0.345 (br, 4H). HRMS (FAB) calcd for $[M + H]^+$ ($C_{23}H_{46}N_3O$) 380.3641, found 380.3640.

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Supporting Information Available: ^{1}H NMR spectra for compounds **1**−**4**, **7**−**15**, and **17**, ^{13}C NMR spectra for compounds **1**, **3**, **4**, **7**−**15**, and **17**, and ^{1}H−^{1}H COSY spectra of compounds **10** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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